

Healing of Excision of wounds on Lower legs by Secondary intention (HEALS) cohort study. Part 1: a multicentre prospective observational cohort study in patients without planned compression

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Abstract

Background. There is no agreed treatment pathway following excision of keratinocyte cancer (KC). Compression therapy is considered beneficial for secondary intention healing on the lower leg; however, there is a lack of supportive evidence. To plan a randomized controlled trial (RCT), suitable data are needed. We report a multicentre prospective observational cohort study in this patient population with the intention of informing a future trial design.

Aim. To estimate the time to healing in wounds healing by secondary intention without planned postoperative compression, following excision of KC on the lower leg; to characterize the patient population, including factors affecting healing; and to assess the incidence of complications.

Methods. This was a multicentre prospective observational cohort study. Inclusion criteria were age ≥ 18 years with planned excision of KC on the lower leg and healing by secondary intention, an ankle-brachial pressure index (ABPI) of ≥ 0.8 ; and written informed consent. Exclusion criteria included planned excision with primary closure, skin graft or flap; compression therapy for another indication; planned compression; inability of patient to receive, comply with or tolerate high compression; or a suspected diagnosis other than KC.

Results. This study recruited 58 patients from 9 secondary care dermatology clinics. In the analysis population ($n = 53$), mean age was 81 years (range 25–97 years), median time to healing was 81 days (95% CI 73–92) and 45 patients (84.9%) had healing of the wound at the 6-month follow-up. The healing prognostic factors were wound parameters and ABPI. Wound infections occurred in 16 participants (30.2%). Four patients (7.5%) were admitted to hospital; three because of an infection and one because of a fall.

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Conclusions. The collected data have informed the RCT preparation. A relatively high proportion (7.5–15%) of unhealed wounds, infection and hospital admissions demonstrate the need for clearly establishing potentially effective treatments to improve outcomes for this population.

Introduction

Skin cancers are common and the numbers are increasing as a result of social change.¹ These cancers are broadly classified into two groups; malignant melanoma (MM), which is less common (incidence 26 in 100 000) but have worse outcomes (mortality rate 3.8 in 100 000) and keratinocyte cancers (KC), which are more common (incidence 245.1 in 100 000) but lead to fewer deaths (mortality rate 1.2 in 100 000).²

There are distinct treatment pathways for MM³ but the treatment and aftercare of KC is less clear. The majority of lower leg KCs are excised and closed surgically under local anaesthetic, but due to the anatomical location, some resulting wounds are left to heal by secondary intention. The resultant longer healing times can impact on patient quality of life (e.g. pain and inconvenience). However, there is very little epidemiological and intervention effectiveness research on surgical wound healing by secondary intention^{4,5} and no standardized methods for the treatment of these wounds on the lower leg.

Compression therapy has been established by primary research and systematic review evidence as the primary/first-line treatment for venous leg ulcers.^{6,7} It reduces oedema, improves venous return and tissue oxygenation, and prevents dressings from moving. It is likely, therefore, that secondary intention healing of surgical wounds on the lower leg might also benefit from compression in a manner similar to healing of venous leg ulcers. A previous survey⁸ of 312 members of the British Society for Dermatological Surgeons (BSDS) showed that 56% of the 109 respondents used compression postsurgery; however, supporting evidence for compression use is underdeveloped. A comprehensive literature search⁹ did not reveal any randomized controlled trials (RCTs) on the use of compression following cutaneous surgery on the lower leg. Suitable data on healing rates in this patient group are not available to inform either clinicians, patients or RCT design.

To successfully deliver a definitive RCT in this cohort, we determined the need to identify healing rates, patient characteristics and complications and to

assess feasibility issues (e.g. recruitment rates and practicalities). The overall aims of the Healing of Excisional wounds on Lower legs by Secondary intention (HEALS) cohort study were to assess the feasibility, safety and acceptability of performing a large-scale definitive Phase 3 trial.

Methods

Study design

This was a multicentre prospective observational cohort study in patients with KC on the lower leg with planned excision of KC and healing by secondary intention. This paper reports the results of the healing data; feasibility data are reported and discussed in a separate publication.

Objectives

The primary objective of the study was to inform the design of an RCT by estimating the time to healing in wounds healing by secondary intention where postoperative compression was not planned following excision of KC on the lower leg. The secondary objectives were to characterize the patient population in relation to factors affecting healing, and to assess the incidence of complications affecting healing.

Setting

Nine UK secondary care dermatology clinics participated. The first centre opened to recruitment in February 2016, and the last centres closed to recruitment in November 2017. The final recorded follow-up assessment took place in June 2018.

Participants

Patients were recruited from secondary care dermatology clinics when attending for planned excision of KC and healing by secondary intention. Assenting eligible patients were identified to the research team and given a patient information leaflet. Participants were free to

withdraw at any time without reason and without prejudicing further treatment.

Eligibility criteria

Inclusion criteria were age ≥ 18 years; planned excision of KC on the lower leg with healing by secondary intention; ankle–brachial pressure index (ABPI) ≥ 0.8 (measured within the previous 3 months); and provision of written informed consent.

Exclusion criteria were planned primary closure, skin graft or flap; receipt of compression therapy for another indication; inability to receive high compression due to ≥ 1 contraindication, on the basis of clinical judgement or local guidelines; inability to comply with or tolerate high compression therapy (delivery of 40 mmHg pressure at the ankle); or suspected non-KC diagnosis.

Planned postoperative compression therapy

Follow-up was performed in standard dermatology clinics until the patient was discharged, and by weekly telephone calls or routine clinic visits until healing or the end of the study (maximum 6 months).

Data collection

Data on the following variables were collected preoperatively: age, sex ethnicity, medical history, medications, mobility, medical specialty involved (Dermatology/Plastic Surgery) and CEAP (clinical, etiological, anatomical, pathophysiological) 2004 classification.¹⁰ Additional information collected postoperatively included details of dressings/bandages/topical applications; unplanned compression; antibiotics; wound area; wound depth; type of wound closure; category of lesion (MM/KC); types of follow-up assessments and follow-up clinical contact; unplanned postoperative compression; complications, including adverse events (AEs); development of crust; healing status; and where possible, clinical confirmation of healing. Details of how the variables were collected and categorized for analysis can be found in Supplementary Data S1.

Data sources/measurement

Information was collected from participants' clinical assessments during routine follow-up visits, medical record review (for actual diagnosis of lesion following surgery) or telephone follow-up with the participant for up to 6 months after registration.

Study size

The sample size was based upon the expected number of recruits at each centre required to provide sufficient data to estimate recruitment feasibility and the healing event rate in the standard-care control arm to inform sample size estimation for an RCT that will compare compression as an adjunct to standard care with standard care alone. The planned target number for recruitment was 55 participants to ensure 50 in the evaluable patient population.

Statistical analysis

Variables were tabulated using frequencies and objective statistics. Missing values were included in tables as 'missing'. The full analysis population was all participants for whom the primary endpoint (time to wound healing) could be defined. The primary outcome was time to wound healing postsurgery (epithelialization). Frequencies of wound-healing status at 6 months postsurgery, median time to healing and corresponding 95% CIs by individual key risk factors and overall are presented together with Kaplan–Meier plots. A sensitivity analysis was conducted, which excluded those with primary wound closure, skin flap or graft. The secondary outcome analyses were incidence of repeat surgery and postoperative complications (presence of infection, hospital admission, delayed discharge, or other) over the study duration, summarized by type of wound closure and overall. Related and unexpected AEs were also reported. Exploratory analyses were the associations between key risk factors (medical history, medications, mobility, ABPI, CEAP classification, wound area, wound depth and type of wound closure) and time to healing, explored using univariable Cox proportional hazards models, provided the proportional hazards assumption did not appear to be violated. ABPI was considered as a continuous variable, while wound area was considered as both a categorical and continuous variable. Estimates of the hazard ratio (HR) and corresponding 95% CI are reported.

Results

Participants

In total, 88 patients were assessed for eligibility, of whom 53 participants were included in the full analysis set (details of exclusions are shown in Fig. 1).

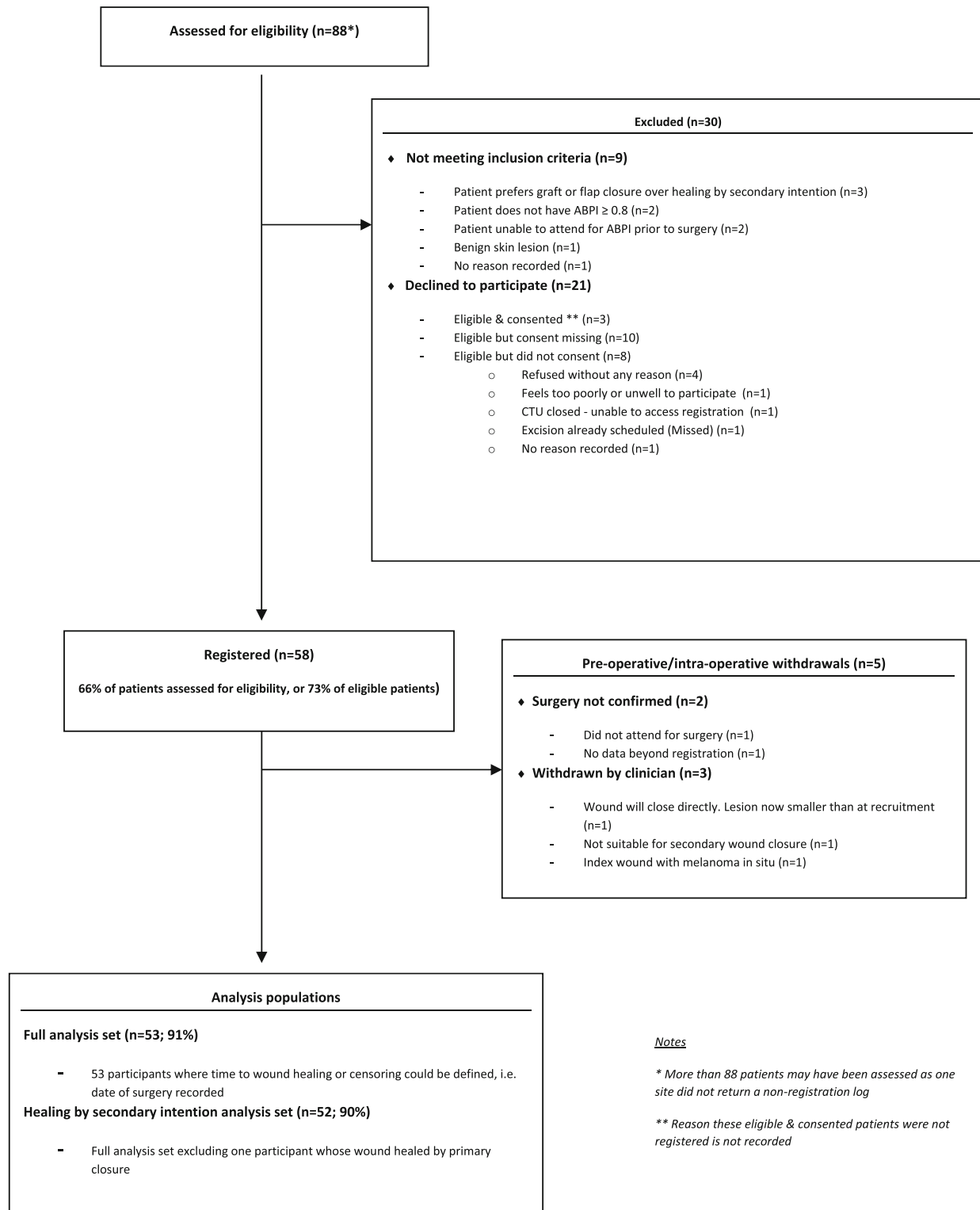


Figure 1 Study flow diagram.

Table 1 Demographics and clinical characteristics.

| Parameter | Result |
|--|------------------------|
| Patients, <i>n</i> (%) | 53 (100.0) |
| Age, years | |
| Mean \pm SD | 79.3 \pm 11.2 |
| Median (range) | 81.0 (25–97) |
| Sex, <i>n</i> (%) | |
| Female | 36 (67.9) |
| Male | 17 (32.1) |
| Ethnicity, <i>n</i> (%) | |
| White | 53 (100.0) |
| Specialty involved, <i>n</i> (%) | |
| Dermatology | 53 (100.0) |
| Plastic surgery | 0 (0.0) |
| Diabetes, <i>n</i> (%) | |
| Yes | 4 (7.5) |
| No | 49 (92.5) |
| Venous ligation/stripping, <i>n</i> (%) | |
| Yes | 3 (5.7) |
| No | 50 (94.3) |
| Hip/knee replacement surgery, <i>n</i> (%) | |
| Yes | 10 (18.9) |
| No | 43 (81.1) |
| Immunosuppressants, <i>n</i> (%) | |
| No | 53 (100.0) |
| Anticoagulants, <i>n</i> (%) | |
| Yes | 15 (28.3) |
| No | 38 (71.7) |
| Mobility, <i>n</i> (%) | |
| Wheelchair-bound | 2 (3.8) |
| Walks with aid | 9 (17.0) |
| Walks unaided | 42 (79.2) |
| ABPI | |
| Patients assessed, <i>n</i> (%) | 51 ^a (96.2) |
| Reading | |
| Mean \pm SD | 1.0 \pm 0.1 |
| Median (range) | 1.0 (0.8–1.5) |
| IQR | 0.9–1.1 |

ABPI, ankle-brachial pulse index; IQR, interquartile range.

^aABPI values were not recorded for two participants although they satisfied eligibility criteria (ABPI \geq 0.8).

Baseline characteristics of participants

Preoperative characteristics. Participant median age was 81 years (range 25–97 years). All patients were white and 36 (67.9%) were women (Table 1).

Immediate postoperative characteristics. Wound depth was characterized as excision to fascia (*n* = 28, 52.8%), excision to fat (*n* = 21, 39.6%) or excision to periosteum (*n* = 35.7%). In total, 22 participants (41.5%) had no wound closure method, while 26 (49.1%) had partial closure with purse string sutures, 2 (3.8%) had pulley sutures and 1 (1.9%) had other partial closure. Only 1 (1.9%) had primary closure reported. Unplanned compression was not used for

Table 2 Postoperative characteristics.

| Parameter | Result, <i>n</i> (%) |
|--|----------------------|
| Wound depth ^a | |
| Excision to fat | 21 (39.6) |
| Excision to fascia | 28 (52.8) |
| Excision to periosteum | 3 (5.7) |
| Missing data | 1 (1.9) |
| Type of wound closure | |
| None | 22 (41.5) |
| Partial closure with purse string suture | 26 (49.1) |
| Partial closure with pulley suture | 2 (3.8) |
| Other: 'partial closure' | 1 (1.9) |
| Other: 'primary closure' | 1 (1.9) |
| Missing data | 1 (1.9) |
| Unplanned compression (initial) | |
| Yes | 0 (0.0) |
| No | 52 (98.1) |
| Missing data | 1 (1.9) |
| Antibiotics immediately prescribed postoperatively | |
| Yes | 10 (18.9) |
| No | 43 (81.1) |
| Medical record review of actual lesion | |
| Melanoma | 0 (0.0) |
| Nonmelanoma | 38 (71.7) |
| Missing data | 15 (28.3) |
| Repeat surgery | |
| No | 42 (79.2) |
| Missing data | 11 (20.8) |

^aExcision to the stated anatomical layer.

any participants. Antibiotics were prescribed for 10 participants (18.9%). Medical record reviews of actual lesions did not reveal any histological MMs (Table 2).

The median postexcision wound area was 6.4 cm² [interquartile range (IQR) 4.4–8.3 cm²]. The median postexcision wound area was larger for partial closure with purse string/pulley sutures or other partial closure (6.9 cm², IQR 5.9–9.8 cm²) than for wounds with no additional closure (4.7 cm², IQR 3.8–6.8 cm²) (Table 3). Repeat surgery was not recorded for any participant.

Follow-up. The median follow-up duration was 79 days (IQR 63–135 days).

Postsurgery

At 6 months postsurgery, 45 of the 53 wounds (84.9%) had healed. Four wounds (7.5%) remained unhealed, and the healing status of the other four wounds (7.5%) was not known (Table 4).

Primary outcome. The median time to healing was 81 days (95% CI 73–92) (Table 5, Fig. 2a), and appeared to be associated with wound depth and wound area. The type of wound closure (none vs. partial) did

Table 3 Wound area assessed.

| Wound area | Overall | Secondary intention healing | | Missing data or primary closure |
|-----------------------------|----------------------|-----------------------------|---------------------------------|---------------------------------|
| | | No additional closure | Additional closure ^a | |
| Postexcision | | | | |
| Assessed, <i>n</i> (%) | 49 (92.5) | 21 (39.6) | 28 (52.8) | – |
| Missing data | 4 ^b (7.5) | 1 (1.9) | 1 (1.9) | 2 (3.8) |
| Wound area, cm ² | | | | |
| Mean ± SD | 7.5 ± 4.8 | 6.9 ± 5.8 | 7.9 ± 4.0 | – |
| Median (range) | 6.4 (1.4–25.9) | 4.7 (2.6–25.9) | 6.9 (1.4–20.5) | – |
| IQR | 4.4–8.3 | 3.8–6.8 | 5.9–9.8 | – |
| Post partial closure | | | | |
| Assessed, <i>n</i> (%) | – | – | 26 (89.7) | – |
| Missing data | – | – | 3 (10.3) | – |
| Wound area, cm ² | | | | |
| Mean ± SD | – | – | 3.9 ± 2.4 | – |
| Median (range) | – | – | 3.1 (0.8–9.5) | – |
| IQR | – | – | 2.2–5.9 | – |

^aPurse string suture, pulley suture or partial closure. ^bReasons for postexcision wound area missing: primary closure (*n* = 1), tracing not completed on ConvaTec grid (*n* = 1), surgeon sterile and unable to do (*n* = 1), no reason given (*n* = 1).

Table 4 Outcome data.

| Wound-healing status at 6 months postsurgery | <i>n</i> (%) |
|--|--------------|
| Healed | 45 (84.9) |
| Not reported as healed | 4 (7.5) |
| Not known | 4 (7.5) |

not affect time to healing. The time to healing for other potential prognostic factors are detailed in Table 5, but sample size precluded detailed interpretation. The sensitivity analysis excluded the one participant who had primary wound closure; otherwise, all results were identical to those in the primary outcome analysis.

Exploratory analyses. The results of fitting univariable Cox proportional hazards models to healing time should be viewed with caution due to the small sample size. Time to healing decreased as ABPI increased (HR = 1.31, 95% CI 1.07–1.60). Time to healing was associated with postexcision wound area: wounds with area < 5 cm² healed more quickly than wounds with area ≥ 5 cm² (HR = 0.48, 95% CI 0.25–0.91), although this effect was diluted when wound area was considered as a continuous variable (HR = 0.95, 95% CI 0.88–1.02). Time to healing also appeared to be associated with wound depth; there was a shorter time to healing for shallower wounds (excision to fat) compared with deeper ones (excision to fascia or periosteum) (HR = 0.46, 95% CI 0.25–0.86) (Table 6).

Postoperative complications and adverse events. Wound infections were recorded for 16 participants (30.2%)

(Table 7). Four participants (7.5%) were admitted to hospital: 3 (5.7%) admitted for related infections, and 1 (1.9%) for a fall. Two of the participants admitted with wound infections both had wound healing at 6 months, while the third still had the wound unhealed at 175 days postsurgery. There were no related or unexpected serious AEs (SAEs).

Discussion

To our knowledge, this is the first study to investigate time to healing in patients with surgical excision of KC of the leg. The study included patients with wounds healing by secondary intention, with no or partial wound closure and we report the extent of AEs. These data should be of use to clinicians currently guiding patients through the consent procedure.

A previous prospective cohort study of all types of surgical wounds healing by secondary intention included 58/396 (14.8%) leg wounds with a median time to healing of 127 days (95% CI 92–210).⁴ This is considerably longer than the present study, but is likely to be a result of that study population having significant comorbidities (20.9% had undergone vascular surgery and 14.5% had peripheral arterial disease), which probably affected healing time. The authors also investigated potential prognostic factors for healing and found wound area (HR 0.46, 95% CI 0.36–0.59) and infection (HR 0.65, 95% CI 0.51–0.84) to be significant predictors of delayed healing.

Our exploratory analysis identified an association with postexcision wound area and time to

Table 5 Median time to healing overall and by key risk factors.

| | <i>n</i> (%) | Median time to healing, days | 95% CI |
|--|--------------|------------------------------|-----------------|
| Overall | 53 (100.0) | 81 | 73–92 |
| Wound depth | | | |
| Excision to fat | 21 (39.6) | 73 | 61–84 |
| Excision to fascia or periosteum | 31 (58.5) | 96 | 75–135 |
| Missing data | 1 (1.9) | – | – |
| Wound area postexcision | | | |
| < 5 cm ² | 16 (30.2) | 71.5 | 56–87 |
| ≥ 5 cm ² | 33 (62.3) | 92 | 79–126 |
| Missing data | 4 (7.5) | – | – |
| Type of wound closure (aggregated categories) | | | |
| Purse string/pulley suture or partial closure | 29 (54.7) | 81 | 63–103 |
| None | 22 (41.5) | 83 | 68–90 |
| Missing data or primary closure | 2 (3.8) | – | – |
| Mobility | | | |
| Bedbound, chairbound or walks with aid | 11 (20.8) | 90 | 50 ^a |
| Walks unaided | 42 (79.2) | 81 | 71–92 |
| Medical history: hip/knee replacement surgery | | | |
| Yes | 10 (18.9) | 85 | 46–113 |
| No | 43 (81.1) | 79 | 70–92 |
| Medications: anticoagulants | | | |
| Yes | 15 (28.3) | 98 | 56–163 |
| No | 38 (71.7) | 79 | 70–90 |
| Postoperative antibiotics | | | |
| No | 10 (18.9) | 68 | 52–87 |
| | 43 (81.1) | 84 | 73–103 |
| CEAP clinical classification | | | |
| C0 | | | |
| Visible or palpable signs of venous disease | 39 (73.6) | 81 | 73–96 |
| No visible or palpable signs of venous disease | 13 (24.5) | 81 | 58–170 |
| Missing data | 1 (1.9) | – | – |
| C1 | | | |
| Telangiectasias or reticular veins | 28 (52.8) | 85.5 | 71–96 |
| No telangiectasias or reticular veins | 24 (45.3) | 79.5 | 61–111 |
| Missing | 1 (1.9) | – | – |
| C2 | | | |
| Varicose veins | 16 (30.2) | 79 | 52–88 |
| No varicose veins | 36 (67.9) | 83 | 70–103 |
| Missing data | 1 (1.9) | – | – |
| C3 | | | |
| Oedema | 21 (39.6) | 89 | 78–136 |
| No oedema | 31 (58.5) | 72 | 62–92 |
| Missing data | 1 (1.9) | – | – |
| C4a | | | |
| Pigmentation or eczema | 19 (35.8) | 81.5 | 71–99 |
| No pigmentation or eczema | 33 (62.3) | 81 | 63–103 |
| Missing data | 1 (1.9) | – | – |
| CEAP: aetiological classification | | | |
| En: no venous cause identified | 17 (32.1) | 83 | 70–142 |
| Ep: primary | 21 (39.6) | 76 | 58–90 |
| Es: secondary (post-thrombotic) | 2 (3.8) | 92.5 | 50–135 |
| Missing data ^b | 13 (24.5) | – | – |

^aInadequate data to calculate confidence limit. ^bOf the 13 participants with missing data for CEAP (clinical, etiological, anatomical, pathophysiological) aetiology, 10 were from a single centre. Of the 11 participants registered at the centre only 1 was not missing value for CEAP aetiology. Note percentages may not sum to 100% due to rounding.

healing. This was expected; however, because of the small numbers, the wound area following partial closure was not used in the analysis and was outside

the scope of this study. There may be an opportunity in the subsequent RCT to investigate the effect of partial closure on wound healing. Although this

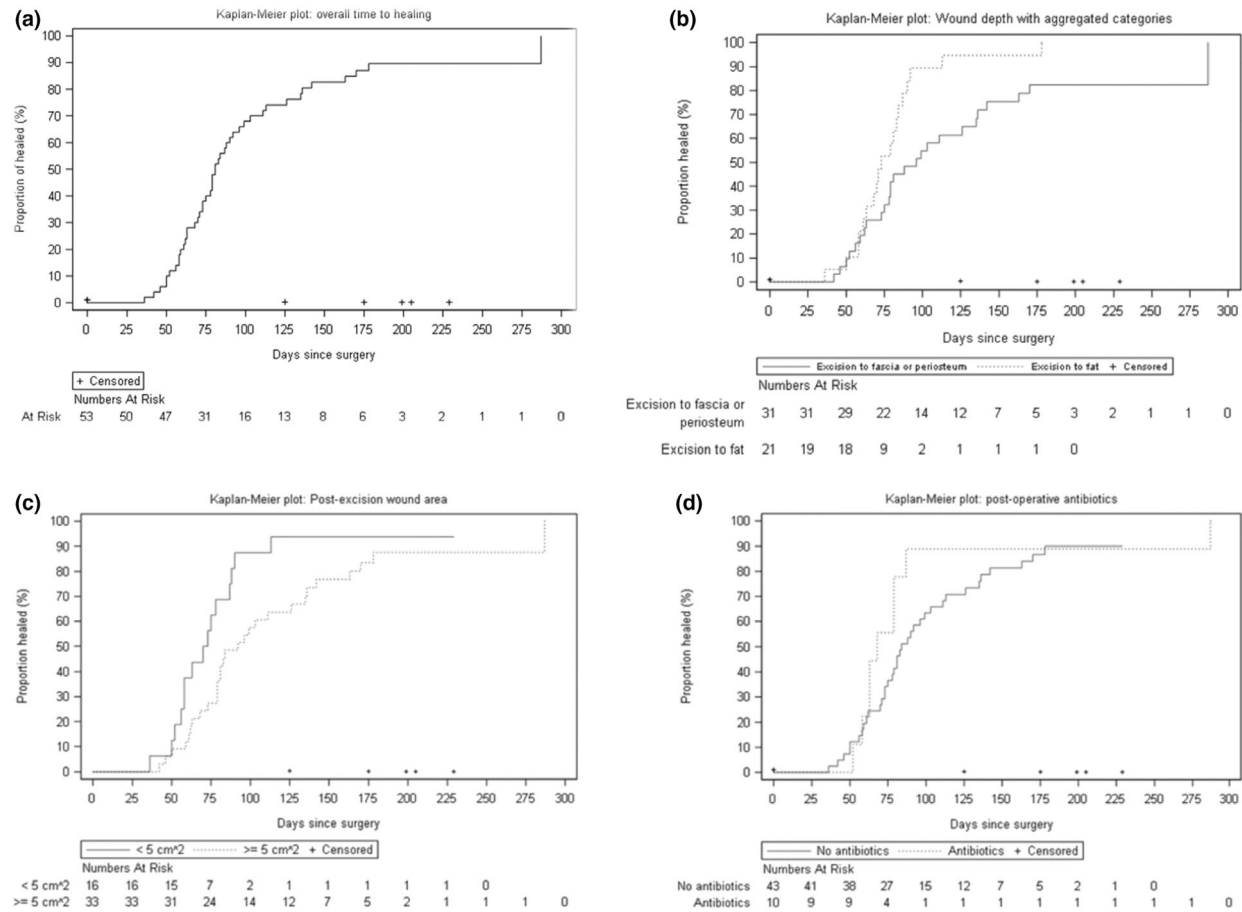


Figure 2 (a–d) Kaplan–Meier plots showing time to healing: (a) overall, (b) by wound depth, (c) by wound area and (d) by postoperative antibiotic prescription.

Table 6 Univariable Cox proportional hazards model results.

| Covariate | HR | 95% CI |
|--|------|-----------|
| ABPI (continuous): per 0.1 unit ABPI | 1.31 | 1.07–1.60 |
| Wound area postexcision (categorical): ≥ 5 cm ² vs. < 5 cm ² | 0.48 | 0.25–0.91 |
| Wound area postexcision (continuous): per 1 cm ² | 0.95 | 0.88–1.02 |
| Wound depth: excision to fascia or periosteum vs. excision to fat | 0.46 | 0.25–0.86 |
| Wound closure: purse string/pulley sutures/partial closure vs. none | 1.08 | 0.59–1.98 |
| Medical history: hip/knee replacement surgery (yes vs. no) | 0.75 | 0.35–1.63 |
| Mobility: bedbound, chairbound, or walks with aid vs. walks unaided | 0.69 | 0.32–1.50 |
| Medications: anticoagulants (yes vs. no) | 0.71 | 0.36–1.39 |
| Medications: postoperative antibiotics (yes vs. no) | 1.54 | 0.71–3.34 |
| CEAP C0: no visible or palpable signs of venous disease (yes vs. no) | 0.84 | 0.41–1.70 |
| CEAP C1: telangiectasias or reticular veins (yes vs. no) | 1.07 | 0.59–1.94 |
| CEAP C2: varicose veins (yes vs. no) | 1.26 | 0.67–2.39 |
| CEAP C4a: pigmentation or eczema (yes vs. no) | 1.04 | 0.56–1.93 |

CEAP, clinical, etiological, anatomical, pathophysiological; HR, hazard ratio.

study had a small number of participants, it was considered that the numbers were sufficient to estimate recruitment and healing rates for an RCT.

A large proportion of patients ($n = 10$) received antibiotics immediately postoperatively. Given the interest in potential prognostic factors for healing in

Table 7 Incidence of postoperative complications during follow-up by type of wound closure.

| Complication | Type of wound closure | | | Total |
|----------------------|---------------------------------|-----------------------|---------------------------------|-----------|
| | Secondary intention healing | | | |
| | Additional closure ^a | No additional closure | Missing data or primary closure | |
| Total | 22 (100) | 29 (100) | 2 (100) | 53 (100) |
| Infection | | | | |
| Yes | 7 (31.8) | 9 (31.0) | 0 (0) | 16 (30.2) |
| No | 14 (63.6) | 20 (69.0) | 0 (0) | 34 (64.2) |
| Missing ^b | 1 (4.5) | 0 (0.0) | 2 (100) | 3 (5.7) |
| Hospital admission | | | | |
| Yes | 3 (13.6) | 1 (3.4) | 0 (0) | 4 (7.5) |
| No | 18 (81.8) | 28 (96.6) | 0 (0) | 46 (86.8) |
| Missing ^b | 1 (4.5) | 0 (0.0) | 2 (100) | 3 (5.7) |

^aPurse string suture, pulley suture or partial closure. ^bThree participants had surgery recorded but no data on follow-up visits.

previous studies^{4,11} and in a retrospective cohort study of wounds,¹² this could be explored in the future RCT.

This study found that 40% of patients had primary venous disease, with a further quarter of the patients having unknown venous status. This study population was not expected to have substantial underlying venous disease, and were required to have adequate arterial supply (ABPI ≥ 0.8). Healing times were consistent with similar comorbid populations.

This study collected data from nine recruiting centres with clinicians performing their usual operative and postoperative techniques. The patient demographics were representative of the population.

Conclusion

This study aimed to inform the design of an RCT to compare compression as an adjunct to standard postoperative care. This aim was met by providing reliable data on healing times, characterizing the patient population, and identifying factors such as infection that can affect healing. This will enable estimation of event rates for an RCT.

What's already known about this topic?

- Very little evidence exists for the effectiveness of wound care interventions for surgical wound healing by secondary intention following excision of nonmelanoma skin cancers (KC) of the lower leg.
- Compression therapy is the first-line treatment for lower leg ulceration but postoperative use

following KC excision is *ad hoc*, with no robust evidence.

- Insufficient information on healing times, patient characteristics and complications are available to plan a trial comparing standard care vs. standard care plus compression.

What does this study add?

- This is the first study to investigate time to healing, infection and SAEs following excision of KC of the lower leg in patients without planned compression.
- Data are provided on healing times, patient characteristics, factors that affect healing, infection rates and SAEs in patients.
- The results highlight the need to optimize treatment effectiveness and outcomes for people following KC excision on the leg.

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Conflict of interest

BW has received honoraria, clinical trial funding or travel scholarships from Abbvie, Lilly, Jansen, Sanofi, Leo and Galderma. The other authors declare that they have no conflict of interest.

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Ethics statement

Ethics approval was given by the South Central – Oxford B Research Ethics Committee (15/SC/0598). Patients provided written, informed consent for participation.

Data availability

Data are available on request from the corresponding author.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Data S1. Variables collected and how they were categorized for analysis.